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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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88/757,770 11/29/96 18

63637-9102

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18N2/1009

EXAMINER

MASOODI, K

ART UNIT	PAPER NUMBER
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1817

DATE MAILED:

10/29/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 11-29-96

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire Three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-29 is/are pending in the application.

Of the above, claim(s) 5, 6, 7, 9, 11, 13, 15, 16-19, 21-27, 29 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-4, 8, 10, 12, 14, 20, 28 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

-- SEE OFFICE ACTION ON THE FOLLOWING PAGES --

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DETAILED ACTION

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. § 121:

Group I Claims 1-4, 8, 10, 12, 14, 20, and 28, drawn to an isolated nucleic molecule encoding TbpA protein, classified in Class 536, subclass 23.1.

Group II Claims 1, 5, 6, 7, 9, 11, 13, 15, 21, and 29, drawn to an isolated nucleic molecule encoding TbpB protein, classified in Class 536, subclass 23.1.

Group III Claims 16-17, drawn to a purified and an isolated TbpA protein, classified in Class 530, subclass 350.

Group IV Claims 18-19, drawn to a purified and an isolated TbpB protein, classified in Class 530, subclass 350.

Group V Claim 22, drawn to an antibody of TbpA protein, classified in Class 424, subclass 130.1.

Group VI Claim 22, drawn to an antibody of TbpB protein, classified in Class 424, subclass 130.1.

Group VII Claims 23-27, drawn to a vaccine comprising TbpA and TbpB, classified in Class 424, subclass 255.1.

The inventions are patentably distinct, each from the other, because:

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Inventions I (or II); III (or IV); and V (or VI); are distinct products, with different chemical structures and different biological properties (i.e immunogenicity).

Inventions I and II are two distinct products having different nucleotide sequences and capable of separate use, manufacture and sale etc..

Inventions I (or II) and III (or IV) are two distinct products. Group I (or II) is comprised of nucleotide sequences while Group III (or IV) is comprised of amino acid sequences and capable of separate use, manufacture and sale etc.

Inventions III and IV are two distinct products having different amino acid sequences and capable of separate use, manufacture and sale etc.

Inventions III (or IV) and V (or VI) are two distinct products having different amino acid sequences and capable of separate use, manufacture and sale etc.

Inventions III (or IV) and VII are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (M.P.E.P. § 806.05(h)). In the instant case, the protein of Group III (or IV) have uses for detection.

Inventions III (or IV) and V (or VI) are related as product and processes of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that

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product (M.P.E.P. § 806.05(h)). In the instant case, the protein of Group III (or IV) have uses for detection.

Because these inventions are distinct for the reasons given above, and a search and examination of the entire application would be a serious burden, the inventions having acquired a separate status in the art as shown by their different classification and/or recognized divergent subject matter, restriction for examination purposes as indicated is proper.

A telephone call was made to James Remenick on September 10, 1997 to request an oral election to the above restriction requirement, and result in an election being made for Group I, claims 1-4, 8, 10, 12, 14, 20, and 28.

Applicant is advised that a complete response to this requirement must include an election of the invention to be examined even though the requirement is traversed.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. § 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. § 1.48(b) and by the fee required under 37 C.F.R. § 1.17(h).

Accordingly, claims 1-4, 8, 10, 12, 14, 20, and 28 are being examined herewith. Claims 5-7, 9, 11, 13, 15-19, 21-27, and 29 are withdrawn from consideration as being non-elected invention.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1-4, 8, and 10, are rejected under 35 U.S.C. 102(b) as being anticipated by Murphy et al (J. Clin. Microbiol. Sept. 1993, vol. 31, no. 9, 2303-2308) .

Murphy et al disclosed isolation and purification of total cell DNA from *Pasteurella hemolytica* and hybridization with a probe (see p. 2304 para 1-3; fig. 1) which is a naturally occurring nucleic acid molecule inherently contains complementary sequences, inherently encodes a transferrin binding protein and capable of hybridizing under stringent hybridization conditions.

Art rejection can be overcome by amending claim by way of example as recited below:

A purified and isolated nucleic acid fragment comprising a nucleic acid sequence as shown in SEQ ID NO: 1.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

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commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4, 8, 10, 12, 14, 20, 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Murphy et al in view of Loosmore et al (IDS: WO 95/13370 May 18, 1995).

Claims are drawn to a purified and isolated nucleic acid molecule encoding a transferrin binding protein of *P. haemolytica*, at least 80% homologous fragments, 15 bases oligo, hybridization under stringent hybridization conditions, a recombinant expression vector adapted for transformation, a host cell, method of preparing transferrin recombinant protein and a vaccine of a recombinant expression vector with a pharmaceutically acceptable carrier.

The teaching of Murphy et al is set forth above which teaches isolation and purification of total cell DNA from *Pasteurella hemolytica* and hybridization with a probe (see p. 2304 para 1-3; fig. 1) which is a naturally occurring nucleic acid molecule inherently contains complementary sequences, inherently encodes a transferrin binding protein and capable of hybridizing under stringent hybridization conditions. Murphy et al does not teach cloning, expression of transferrin binding protein and a vaccine.

Loosmore et al teaches cloning, hybridization under stringent hybridization conditions, expression of a transferrin binding protein and use of said recombinant expression vector as a

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vaccine in a pharmaceutically acceptable carrier for the treatment of Haemophilus infection (see abstract; p. 7 lines 4-35, p. 9, lines 1-15, examples 2-21; summary of the invention p. 67, claims and entire document). Loosmore et al does not specifically teaches that a recombinant expression vector comprising a nucleic acid molecule and one or more transcription and translation elements operatively linked to the nucleic acid molecule. However, expression cassettes or constructs taught in examples 19-21, 8-10 contains one or more transcription and translation elements operatively linked to the nucleic acid molecule, without these elements protein cannot be expressed and it is known to one of ordinary skill in the art.

It would have been obvious to one of ordinary skill in the art at the time of invention was made to purify and isolate nucleic acid molecule encoding a transferrin binding protein of Pasteurella hemolytica and express, hybridize, prepare oilgo and use recombinant molecules as vaccine in a pharmaceutically acceptable carrier as suggested by Loosmore et al. One would have been motivated to do so because this is within the level of one of ordinary skill in the art to simply substitute routinely used procedures performed by Loosmore et al for a transferrin binding protein from Haemophilus to another bacterial pathogen Pasteurella hemolytica of Murphy et al because both the organisms share and/or expected to have sequence homology. The invention as a whole is prima facie obvious.

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4. Claims 4, 8, 10, 12, 14, 20, 28 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is vague and indefinite in the recitation of "comprises a nucleic acid sequence; nucleic acid sequences complementary to nucleic acid sequences; at least 80% homologous to (a); or a fragment; stringent hybridization conditions" because a nucleic sequence of SEQ ID NO: 1 as recited encompasses indefinite number of nucleic acid molecules therefore, metes and bounds of claims are unclear. The meaning of "homologous" term is not clear. The term "homology" does not have a single defined meaning in the art. Homology has the precise meaning of having a common evolutionary origin but also conveys the loose meaning of possessing similarity or being matched. Homology is not a quantitative property. Therefore, intended level of identity between the referenced sequences is unclear and metes and bounds of claims are unknown. It is not clear whether one given nucleotide sequence encodes said protein or proteins or different nucleotide sequences encode different proteins. It is also unclear whether claims are drawn to mixture by nucleic acid molecules. The term "stringent hybridization conditions" is unclear as to what stringent conditions will permit to hybridize an isolated transferrin binding protein encoded by a nucleic acid molecule with an isolated nucleic acid molecule. The lack of clarity with respect to what conditions e.g. of temperature, salt etc are considered to be stringent and thus as to what degree of mismatch exist between claimed isolated nucleic acid molecule and SEQ ID NO: 1. Also, there is no specific sequence recited in claim 1 which serves as a reference point.

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Claim 12 is vague and indefinite in the recitation of “one or more” transcription and translational elements because it is indeterminate.

5. Claims 1-4, 8, 10, 12, 14, 20, 28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a TbpA of SEQ ID NO. 1 or SEQ ID NO: 2, does not reasonably provide enablement for an isolated and purified nucleic acid molecule comprising a sequence, nucleic acid sequences complementary to nucleic acid sequences; at least 80% homologous to; or a fragment; stringent hybridization conditions and 15 contiguous bases of nucleic molecule which includes an indefinite number of nucleic acid molecules encoding proteins having different structural and biological activities of unknown nature, from only limited example of the specification represented as SEQ ID NO.1, it is unknown and unpredictable as to how SEQ ID NO. 1 nucleic acid molecule would compare with other transferrin binding proteins in terms of structural and biological activities. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. One cannot apply the teaching of specification from one example to get other variants, in the absence of such information one of skill in the art would not be able to obtain, or predict how to modify and retain the structural and biological properties of, all of the transferrin binding polypeptides as a vaccine for the prophylaxis and treatment of an infection caused by a *Pasteurella* spp encompassed in the claims without undue experimentation. Indeed, on p. 55-56, lines 10-12 of the specification, applicant states that vaccination with Tbp1

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alone was of no benefit after experimental challenge therefore, it is unpredictable in the art that all kinds of uncharacterized recombinant molecules will be useful as a vaccine for the treatment of an infection caused by a wide variety of a *Pasteurella* spp. Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduce the biological activity of the mitogen (see Lazar et al.). Fox et al. U.S. Patent No. 4,879,213 teach methods for identifying antigenic determinants are unpredictable, because there is no reliable method which determines which linear segments are accessible to the host's immune system and linear peptides do not mimic the secondary and tertiary structures (see col. 3, lines 5-20). These references demonstrate that a even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein and the methods for identifying fragments are unpredictable. In view of lack of guidance, lack of examples, and lack of predictability associated with regard to expressing proteins, inducing an immunological response and using the myriad of fragments encompassed in the scope of the claims one skilled in the art would be forced into undue experimentation in order to practice broadly the claimed invention.

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It is suggested the claims should be directed to enabled nucleic acid molecule encoding transferrin binding protein of SEQ ID NO.1 or SEQ ID NO:2.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khalid Masood whose telephone number is (703) 305-6998.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 180 by facsimile transmission via the PTO Fax Center, located in Crystal Mall 1. The Fax Center number is (703) 308-4242. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

If attempts to reach the examiner by telephone are unsuccessful, the examiners's supervisor, Dr. Paula Hutzell, can be reached on (703)308-4310.


Khalid Masood, Ph.D.
September 30, 1997


PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER
GROUP 1800